MicroRNA programs in normal and aberrant stem and progenitor cells.

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Public Summary:
Stem cells have the ability to self-renew or differentiate into specific lineages. Discovering the means by which they accomplish these feats brings us closer to realizing the promise of these cells in regenerative medicine. In this study we analyzed the expression of a class of small RNA molecules, microRNAs (miRNAs), in multiple adult tissue stem cells before and after their exit from the stem cell state. MiRNAs repress multiple genes and provide an additional layer of gene regulation prior to protein translation, and we have yet to study those miRNAs utilized by stem cells. Our analyses revealed miRNAs common or unique to blood, muscle, and neural stem cell populations that change during the early differentiation process. We identified a subset of miRNAs that increase during the exit from a self-renewing state in multiple adult tissue stem cells and were also changed by mutations and cancers that altered stem cell properties. When we forced the expression of these miRNAs in stem cells, they diminished their stem cell activity and targeted genes required for stem cell self-renewal. This study lays a foundation for understanding the role of miRNAs in stem cells and demonstrates that adult tissue stem cells up-regulate miRNAs that target key self-renewal genes as they differentiate.

Scientific Abstract:
Emerging evidence suggests that microRNAs (miRNAs), an abundant class of approximately 22-nucleotide small regulatory RNAs, play key roles in controlling the post-transcriptional genetic programs in stem and progenitor cells. Here we systematically examined miRNA expression profiles in various adult tissue-specific stem cells and their differentiated counterparts. These analyses revealed miRNA programs that are common or unique to blood, muscle, and neural stem cell populations and miRNA signatures that mark the transitions from self-renewing and quiescent stem cells to proliferative and differentiating progenitor cells. Moreover, we identified a stem/progenitor transition miRNA (SPT-miRNA) signature that predicts the effects of genetic perturbations, such as loss of PTEN and the Rb family, AML1-ETO9a expression, and MLL-AF10 transformation, on self-renewal and proliferation potentials of mutant stem/progenitor cells. We showed that some of the SPT-miRNAs control the self-renewal of embryonic stem cells and the reconstitution potential of hematopoietic stem cells (HSCs). Finally, we demonstrated that SPT-miRNAs coordinately regulate genes that are known to play roles in controlling HSC self-renewal, such as Hoxb6 and Hoxa4. Together, these analyses reveal the miRNA programs that may control key processes in normal and aberrant stem and progenitor cells, setting the foundations for dissecting post-transcriptional regulatory networks in stem cells.